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PRINCIPAL INVESTIGATOR: Jennifer L. Kelsey, Ph.D.
                        Esther M. John, Ph.D.*

CONTRACTING ORGANIZATION: Stanford University
                          Stanford, CA 94305-5092

                          * Northern California Cancer Center
                            Union City, CA 94587
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Jennifer L. Kelsey, Ph.D. (nominal PI)

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13. ABSTRACT (Maximum 200

Few epidemiologic studies to date have addressed the hypothesis that Vitamin D reduces breast cancer risk. We analyzed interview data obtained from a cohort of white women aged 25-74 years who participated in the first National Health and Nutrition Examination Survey (NHANES I) from 1971 to 1975 and were followed until 1987. We performed Cox proportional hazards analysis to assess the relationship between sunlight exposure, dietary vitamin D intake, and supplement use and breast cancer risk. The analytic cohort comprised 133 women diagnosed with breast cancer during follow-up and 4,748 women without a self-reported history of breast cancer. Reduced breast cancer risk was associated with high sunlight exposure assessed by the examining physician (RR=0.60, 95% CI=0.33-1.09) and self-report (RR=0.54, 95% CI=0.28-1.02), high solar radiation in state of longest residence (RR=0.59, 95% CI=0.36-0.94), residence in the South at baseline (RR=0.59, 95% CI=0.35-0.98), and dietary intake of more than 206 IU assessed by 24-hour dietary recall (RR=0.67, 95% CI=0.40-1.11). Actinic skin damage, an indirect measure of sunlight exposure, and regular use of multivitamins were not associated with breast cancer risk. Adjustment for other risk factors only minimally changed the relative risk estimates. These findings support the hypothesis that vitamin D may reduce breast cancer risk and warrant future epidemiologic studies.

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VITAMIN D AND BREAST CANCER

FINAL REPORT

PREPARED BY:

Jennifer L. Kelsey, Ph.D.

ESTHER M. JOHN, PH.D.

PRINCIPAL INVESTIGATOR (s)

NORTHERN CALIFORNIA CANCER CENTER

UNION CITY, CA

Esther M. John, Ph.D.

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1. INTRODUCTION

1.1. Nature of the problem

Breast cancer mortality rates for both black and white women are higher in the Northeast than in the South of the United States [1]. Although the geographic variation has somewhat diminished over time, as more areas in the South have experienced rising mortality rates than in the North [2], state-level mortality rates in 1985 to 1989 were still about 50% higher in the Northeast than in the South [1].

Few studies to date have attempted to explain the geographic variation of breast cancer mortality rates in the United States. A north-south gradient is not evident for most other cancers [3]. Therefore, the observed geographic variation is unlikely to be due solely to regional differences in death certification. An analysis of county-level breast cancer mortality rates found only weak correlations with income, level of urbanization, and birth rates among young women [4]. A new correlation study published in late 1995 reported that most of the differences in mortality rates between the Northeast and the South were explained by regional differences in reproductive risk factors [5]. The authors, however, concluded that regional differences in exposure to environmental factors such as vitamin D, sunlight exposures, pesticides etc., may account for the remaining geographic differences in mortality rates.

1.2. Vitamin D hypothesis

In 1990, an ecologic correlation study reported a strong inverse association between breast cancer mortality rates and solar radiation, the major source of vitamin D [6]. Based on these findings and experimental evidence of anti-tumor effects of the vitamin D metabolite 1,25-dihydroxyvitamin D (1,25(OH)2D), Garland et al. hypothesized that vitamin D or its metabolite 1,25(OH)2D may reduce the risk of breast cancer [6].

Serum vitamin D derives from three sources: Vitamin D is synthesized in the skin following sunlight exposure and is absorbed from the diet (e.g., fatty fish, liver, eggs, dairy products; fortified milk, breakfast cereals, and margarine) and supplements. It is, however, inert and through successive hydroxylations in the liver and kidney, vitamin D is converted to 25 hydroxyvitamin D (25(OH)D), and 1,25(OH)2D, which is the biologically active metabolite [7]. Sunlight is the major source of vitamin D. Besides the length of time spent outdoors, a number of factors affect the cutaneous synthesis of vitamin D, including environmental factors (e.g., geographic latitude, altitude, season of the year, time of day, atmospheric conditions), host factors (e.g., age, skin pigmentation), and behavioral factors (e.g., use of protective clothing, sunscreen) [7].

The strongest evidence supporting the plausibility of the vitamin D hypothesis stems from experimental studies. Over the past 10 to 15 years experimental evidence has accumulated on the anti-cancer effects of vitamin D. Both *in vitro* and *in vivo* studies have demonstrated that 1,25(OH)2D inhibits the proliferation and promotes the differentiation of many types of normal and malignant cells, including breast

cancer cells [8-10]. The action of 1,25(OH)2D is mediated through specific intracellular receptors that have been identified in many cell types [11, 12], including breast cancer cells [13]. A number of vitamin D analogs have recently been developed that also inhibit cell proliferation *in vitro* and *in vivo*, but with a fraction of the calcemic activity of 1,25(OH)2D [14, 15]. Vitamin D analogues therefore may have important future use in chemoprevention [16].

Aside from ecologic correlations with solar radiation in the United States [6] and in the former Soviet Union [17, 18], air pollution in Canada [19], and fish consumption [20], epidemiologic data on the relationship between breast cancer risk and dietary sources of vitamin D (e.g., fish) are sparse and inconsistent [21-23]. No study to date has examined the association with sunlight exposure.

With regard to serum vitamin D metabolite levels, a north-south gradient and pronounced seasonal variation (especially in northern latitudes) are seen for serum levels of 25(OH)D which is immediately affected by sunlight exposure and dietary vitamin D intake [7, 24]. In contrast, serum levels of 1,25(OH)2D are relatively stable [7, 24], but some studies suggest that serum levels of 1,25(OH)2D may vary seasonally [25, 26] and among populations with different exposure to solar radiation [27]. Two recently published abstracts reported conflicting results on the relationship between breast cancer risk and serum levels of 1,25(OH)2D [28, 29].

1.3. Purpose of present work

The purpose of this study was to test the hypothesis that high exposure to vitamin D is associated with reduced breast cancer risk. The availability of data from a follow-up study of a national cohort presented a cost-effective way to explore the vitamin D hypothesis. The baseline interview obtained data which offered the opportunity to examine the relation between breast cancer risk and vitamin D from multiple sources, including sunlight exposure, residential solar radiation, and vitamin D intake from diet and supplements.

1.4. Significance

Breast cancer is the leading incident cancer in the United States, affecting one in nine women over their lifetimes, and accounting for 32% of all newly diagnosed cancers in women. Yet the etiology of breast cancer is not well understood. As recently summarized [30], the most consistently reported risk factors for breast cancer include menstrual and reproductive characteristics, such as early menarche, late age at first full-term pregnancy, low parity, and late age at menopause. Other established risk factors include high education, postmenopausal obesity, a family history of breast cancer, a personal history of benign breast disease, and ionizing radiation to the chest. These risk factors, however, account for less than half of the incidence of breast cancer [31, 32]. In addition, few of the established risk factors are potentially modifiable through behavioral or environmental changes. Epidemiologic research into new risk factors for breast cancer is clearly needed in order to prevent this important cause of morbidity and mortality. This study addresses the role of vitamin D, a newly hypothesized risk factor which is potentially modifiable.

2. BODY

2.1. Materials and Methods

2.1.1. Study design and population

The first National Health and Nutrition Examination Survey (NHANES I) collected extensive health and nutritional data on a multistage, stratified probability sample of 23,808 US residents between 1 and 75 years of age. The survey oversampled populations at highest risk for malnutrition (i.e., persons of low income, women of childbearing age, and persons 65 years and older). Baseline data were collected between 1971-75 by in-person interview (including demographic and socioeconomic background, medical history, 24-hour dietary recall, supplement use), medical examinations (including dermatologic examination), and laboratory tests [33, 34].

Adult NHANES I participants aged 25-74 years, including 8,596 women and 5,811 men, were followed for subsequent development of various health conditions and mortality [35-37]. The first follow-up survey conducted in 1982-84 tried to trace and contact all participants of the baseline interview and examinations. The 1986 follow-up survey was conducted among NHANES I participants who were between 55 and 74 years of age at baseline and who were alive during the 1982-84 follow-up survey (N = 3,980). The third follow-up survey conducted in 1987 included individuals who were not identified as deceased in the two previous follow-up surveys (N = 11,750). By the end of the third follow-up survey, 732 (5.1%) subjects of the original cohort (N = 14,407) could not be traced and 937 (6.5%) individuals refused to participate in any of the follow-up interviews.

Follow-up data were collected through in-person interviews (in 1982-84) or telephone interviews (in 1986 and 1987) with surviving individuals or proxy respondents, health care facilities medical records and death certificates. For all medical conditions ascertained in the interview, information was requested on overnight hospital stays from 1970 to the time of follow-up. For all reported hospitalizations, medical records were sought to determine hospital admission and discharge dates and discharge diagnoses. For malignancy-related admissions, pathology reports were requested. For deceased individuals, death certificates were sought to determine date and cause of death.

2.1.2. Outcome definitions

Women who were diagnosed with breast cancer between the baseline interview and 1987 were identified from the follow-up interviews, hospital records, or death certificates. Data from these three sources were carefully reviewed for any mention of breast cancer. The 1982-84 interview asked about histories of cancerous or malignant lumps of cysts in the breast, breast biopsies, and mastectomies, as well as about cancer diagnoses since the baseline interview. The 1986 and 1987 interviews only inquired about cancer diagnoses since last follow-up.

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A total of 240 women had some mention of breast cancer in at least one of the three data sources. Of these, 157 women were hospitalized for breast cancer (N = 148) or died from breast cancer (N = 9) during the follow-up period. These breast cancers included 148 self-reports confirmed by hospital records, 5 proxy-reports confirmed by death certificates, and 4 reports on death certificates only.

An additional 33 women were identified whose self-reports of breast cancer were not confirmed by hospital records. Eighteen of these women reported to have had breast cancer and reported a year of diagnosis following the year of the baseline interview. Fifteen women reported either having had a malignant lump or cyst in their breast and/or a mastectomy and a single biopsy received during the follow-up period. Not all hospitals participated in the submission of medical records for hospitalizations reported by study participants which partly explains the lack of confirmation through hospital records. We therefore did not limit the breast cancers to those confirmed through medical records.

Fifteen women reported a diagnosis of breast cancer prior to the baseline interview, and were therefore treated as prevalent cases. Thirty-five women reported a malignant lump or cyst in their breast and/or a mastectomy, but did not provide a year of diagnosis or year of first breast biopsy. Since it could not be determined whether these were prevalent or incident breast cancer cases they were treated as ambiguous cases.

2.1.3. Exposure variables

2.1.3.1. Vitamin D from sunlight exposure

The baseline interview and dermatologic examination collected information on several variables which we used as direct or indirect measures of sunlight exposure.

a) Usual sunlight exposure: Three questions directly assessed usual sunlight exposure which we used to test our main hypothesis that women with high sunlight exposure have a lower risk of breast cancer.

As part of the dermatologic examination at baseline, each participant was questioned by the examining physician about the amount of time spent outdoors at work and during leisure time. This information was obtained prior to conducting the clinical examination. Each participant's sunlight exposure was classified by the physician as considerable, moderate, or unimpressive.

The 1982-84 follow-up interview asked participants to separately classify their usual occupational and recreational sunlight exposure as never, rare, occasional, or frequent. A composite measure of overall sunlight exposure (low, medium, high) was constructed by cross-classifying self-reported occupational and recreational sunlight exposure.

b) Personal characteristics: Individuals whose skin burns when exposed to sunlight may be more likely to avoid sunlight exposure. The baseline interview

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inquired about each participant's natural hair color at age 20 years and eye color. Using this information as an indirect measure of sunlight exposure, we hypothesized that women with blonde or red hair or blue eyes have less sunlight exposure and therefore a higher risk of breast cancer compared to women with dark hair or dark eyes.

c) <u>Actinic skin damage</u>: Among whites, actinic keratosis and other types of actinic skin damage have been associated with cumulative sunlight exposure [38-40]. In the baseline clinical examination of the skin and subcutaneous tissue, each participant's overall actinic skin damage was classified as absent, minimal, moderate, or severe. The same classifications were provided for actinic keratosis, fine telangiectasia, and senile elastosis. We used the degree of actinic skin damage as an indirect measure of sunlight exposure, hypothesizing that women with moderate or severe actinic skin damage would have had more sunlight exposure and therefore have a lower risk of breast cancer compared to women without actinic skin damage.

c) <u>Residential sunlight exposure</u>: Geographic latitude is an important determinant of cutaneous vitamin D synthesis. At high latitudes such as Boston, the intensity of solar radiation during the winter months is not sufficient for the synthesis of vitamin D [41]. We therefore considered solar radiation as another indirect measure of sunlight exposure, hypothesizing that women living in areas with high solar radiation or in the South are at lower risk of breast cancer compared to women living in areas with low solar radiation or in the Northeast.

The baseline interview recorded information on region of residence at baseline (South, West, Midwest, Northeast), state of longest residence, and duration of residence in that state. We assigned each state an average solar radiation level and used it as a surrogate measure for ultraviolet B radiation exposure. Data on solar radiation are available for 235 National Weather Service Stations in the US [42]. For states with more than one station, we computed average solar radiation levels. Based on the tertile distribution, the solar radiation in each state was classified as low (<305 Langleys), medium (305-365 Langleys), or high (> = 366 Langleys).

To account for differences in duration of longest residence, we restricted a subanalysis to women who spent 20 or more years or at least 50% of their lifetime in the state of longest residence. Solar radiation in state of birth was used as a surrogate measure of childhood sunlight exposure.

d) <u>Occupational sunlight exposure</u>: The baseline interview inquired about each participant's job held during the 2 weeks prior to the interview. However, only 43% of women were employed at baseline and only 62 women (including 1 breast cancer case) worked in an occupation which was rated as predominantly outdoors by two industrial hygienists. This variable was therefore not deemed suitable for analysis.

2.1.3.2. Dietary vitamin D

The baseline interview included a 24-hour dietary recall and a food frequency questionnaire which assessed for the 3 months preceding the interview the usual

frequency of consumption of selected food items, including the following dietary sources of vitamin D: whole milk, skim milk, fish, eggs, and cheese.

In order to estimate the dietary vitamin D intake from the 24-hour recall data, we had to add vitamin D to the NHANES I nutrient database. We first conducted an extensive review and comparison of vitamin D values listed in published nutrient tables by Pennington [43], Bowes and Church [44-48], McCance and Widdowson's [49], and the US Department of Agriculture [50]. We reviewed several nutrient databases which provide vitamin D values, including the U.C. Berkeley Minilist, the nutrient database used by Dr. Jean Hankin at the Cancer Center of the University of Hawaii, the nutrient database of the Willet food frequency questionnaire, and the Minnesota Nutrition Data System. Without success we tried to obtain information from the USDA on the research papers from which they derived the vitamin D values presented in the USDA provisional table. Lastly, we consulted with several nutritionists affiliated with the various databases to learn about the sources and methodologies used in assigning vitamin D nutrient values.

Our comparison focused on the major sources of naturally occurring vitamin D such as fatty fish, eggs, and liver. Small amounts of vitamin D are also found in lean fish, shellfish, unfortified milk, and dairy products such as cheese, butter, and cream. Fat content, and thus vitamin D content of many fish varies considerably by season and location (Pacific vs Atlantic) of landing [49]. None of the nutrient tables contains a comprehensive list of all types of fish, including fish prepared by different methods (e.g., raw, cooked, canned, smoked). Thus nutrient databases typically rely on substitutions for fish with unknown vitamin D values.

Comparing vitamin D values for fish from various nutrient tables and databases, we found considerable variation in vitamin D values, as well as inconsistencies and apparent errors in substitutions. Our research efforts and communications with various nutritionists clearly demonstrate a lack of research on vitamin D nutrient values.

To assign vitamin D nutrient values to all relevant foods and mixtures of foods reported in the 24-hour diet recall, we used the vitamin D values provided in the 1991 USDA provisional tables of vitamin D content. For fish not included in the USDA provisional table and other sources, we assigned vitamin D values based on fat content, similar to the approach used in the Minnesota Nutrition Data System. Due to lack of data, we assigned identical vitamin D values for a specific fish prepared by different methods (e.g., canned vs smoked).

For foods fortified with vitamin D (e.g., milk, cereal, and margarine), vitamin D values are provided in the 1994 edition of Bowes and Church [48] and the USDA provisional table [50]. However, fortification practices may change over time. We therefore contacted the major manufacturers of breakfast cereals (i.e., Kellogg's, Quaker Oats Company, General Mills, Kraft General Foods) and margarine and requested for specific products information on amount of vitamin D fortification and year when fortification started. Based on the fortification practices in the early 1970s, we assigned vitamin D values to specific brand name cereals listed in the 24-hour recall data file. Since only two types of margarine were fortified with vitamin D

in the 1970s and since the 24-hour recall data file did not list specific types of margarine consumed, we did not add any fortification level to margarine.

To assign vitamin D values to all the foods reported in the dietary recall, we used a cross-reference file developed by Dr. Suzanne Murphy from the University of California at Berkeley. This cross-reference file assigns vitamin D values from the U.C. Berkeley Minilist (a 195 item nutrient database which contains vitamin D) to the 3,527 food codes from NHANES I, using substitutions for foods not included in the Minilist or combinations of Minilist food codes (recipes) for mixtures of foods (e.g., seafood dish) [51, 52]. After modifying some of the vitamin D values in the Minilist to match those in the USDA provisional table and some of the substitutions in the cross-reference file, we applied these modified files to the 24-hour dietary recall data and estimated the dietary vitamin D intake for each member of the analytic cohort. Based on the quartile distribution of the analytic cohort, each person's vitamin D intake was classified as very low (< 44 IU), low (44-110 IU), medium (111-206 IU), or high ($>= 207$ IU).

2.1.3.3. Vitamin D from supplements

The baseline dietary interview also inquired about the frequency of supplement use (regular use, irregular use, no use) and the type of supplement used. Regular use was defined as daily use and irregular use as at least once a week. Since the public use tape coded only one type of supplement for each supplement user, we obtained from the Division of Cancer Prevention and Control at the National Cancer Institute a file with complete data on all supplements used.

2.1.3.4. Summary of exposure variables

The following exposure variables were examined in the main analyses:

Type of exposure	Coding
Sunlight exposure	
1. physician-determined sunlight exposure	considerable, moderate, unimpressive
2. self-reported usual recreational sunlight exposure	frequent, occasional, rare or never
3. self-reported usual occupational sunlight exposure	frequent, occasional, rare or never
4. overall usual sunlight exposure (recreational and occupational)	high, medium, low
Personal characteristics	
5. natural hair color at age 20	black, dark brown, brown, red/blonde
6. eye color	dark brown, light brown, gray/green, blue
Residential exposure to solar radiation	
7. region of residence at baseline	South, West, Mid-West, Northeast
8. solar radiation in state of longest residence	high, medium, low (tertiles)
9. solar radiation: 20+ years of residence	high, medium, low (tertiles)
10. solar radiation: 50+ % of lifetime residence	high, medium, low (tertiles)
11. solar radiation in state of birth	high, medium, low (tertiles)
Dietary vitamin D	
12. vitamin D intake (24-hour recall)	high, medium, low, very low (quartiles)
13. whole milk: frequency of consumption	7+ /wk, 1-6 /wk, never or <1 /wk
14. skim milk	7+ /wk, 1-6 /wk, never or <1 /wk
15. fish	2+ /wk, 1 /wk, never or <1 /wk
16. eggs	3+ /wk, 1-2 /wk, never or <1 /wk
17. cheese	3+ /wk, 1-2 /wk, never or <1 /wk
Vitamin D from supplements	
18. multivitamins	regular, irregular, never
19. multivitamins or single vitamin D	regular, irregular, never
Overall vitamin D exposure	
20. vitamin D from sunlight and diet	high, medium, low

2.1.4. Confounder variables

The baseline interview collected information on various other risk factors for breast cancer which we considered as potentially confounding variables in the analysis, including age at baseline, education, marital status, family income, age at menarche, frequency of alcohol consumption during the year preceding the baseline interview, and recreational and occupational physical activity. An overall index of physical activity was created by cross-classifying levels of recreational and occupational physical activity. Weight and height were measured at baseline using standardized procedures. Body mass index was calculated as weight (kg)/height (m)^2 . Two additional potentially confounding variables, family history of breast cancer and age at first birth, were derived from the first follow-up interview in 1982-84.

Associations of these variables with breast cancer risk were evaluated and the following variables were included in the multivariate analyses: education (less than 12 years, 12 years, 13 or more years), family income (quartiles), body mass index (quartiles), frequency of alcohol consumption during the year preceding the baseline interview (less than once a month or never, once a month to several times a week, almost daily or daily), and overall physical activity (inactive, moderate, very active). The cut-points for the quartiles were based on the distribution of the risk factors in the analytic cohort.

2.1.5. Analytic cohort

Data on outcome, exposures, and other risk factors were extracted from 14 public use data tapes and a single analytic data file was constructed. The analytic cohort was established following a series of exclusions. Of the 8,596 women aged 25-74 with baseline data, 814 (13.8%) could not be traced or refused to participate in any of the three follow-up surveys and were considered lost to follow-up (table 1). Women were excluded from the analytic cohort if they reported a prior history of malignancy at baseline (N = 235), a diagnosis of breast cancer prior to the baseline interview (N = 15), or ambiguous or incomplete data regarding the year of breast cancer diagnosis (N = 35), leaving 190 incident cases of breast cancer and 7,307 women without a self-reported history of breast cancer. The dietary assessment and dermatologic examination were performed only during the first 4 years of NHANES I. These data were therefore available only for 157 breast cancer cases and 5,787 women without breast cancer. The breast cancer cases included too few black women (N = 24) for a separate analysis (table 2). We therefore limited the analysis to white women, comprising 133 breast cancer cases and 4,748 women without a self-reported history of breast cancer.

The size of the analytic cohort further varied by type of exposure variables and type of confounders included in the analysis. For *sunlight-related exposure variables*, data were available for 133 breast cancer cases and 4,748 women without a self-reported history of breast cancer. Analyses which adjusted for a history of breast cancer and age at first birth were based on 120 breast cancer cases and 4,226 women without breast cancer, since these analyses were limited to women who completed the first follow-up interview in 1982-84.

Analyses of *diet-related exposure variables* were based on 127 breast cancer cases and 4,561 women without breast cancer, after excluding individuals who were pregnant or breast-feeding at the time of the 24-hour dietary recall, who were pregnant during the 3 months preceding the baseline dietary assessment, or whose dietary data were provided by a proxy respondent or considered unsatisfactory by the interviewer. Adjustment for family history of breast cancer and age at first birth reduced the analysis to 114 breast cancer cases and 4,097 women without breast cancer.

2.1.6. Statistical methods

Members of the analytic cohort were first classified by sunlight and dietary exposure status at baseline using the exposure variables defined in section 2.1.3.4. To evaluate the relationships between baseline exposure to vitamin D from sunlight, diet, and supplements and subsequent risk of breast cancer, we performed Cox proportional hazards regression analyses using the SAS PHREG procedure.

For women with breast cancer, we estimated the person-years of follow-up from the date of the NHANES I interview/examination to the incidence date of breast cancer. The following dates have been used as the breast cancer incidence date: the date of first hospital admission for breast cancer for self-reports confirmed by hospital records, the mid-point of the self-reported year of diagnosis (June 30) for self-reports without hospital record confirmation, and the date of death for the breast cancers confirmed by death certificates only. For women without breast cancer, the person-years of follow-up have been estimated from the date of the NHANES I interview to the date of last interview if alive or to the date of death if deceased. Average follow-up for the analytic cohort was 13.6 years.

We first computed age-adjusted relative risks and 95% confidence intervals for each of the sunlight and dietary exposure variables. We then individually adjusted the relative risks for potentially confounding variables, including education, income, body mass index, alcohol consumption, physical activity, age at first birth, and family history of breast cancer. Confounding was assessed by comparing the age-adjusted relative risks derived from models with and without the risk factor under evaluation.

To assess potential confounding by multiple risk factors, we performed two sets of multivariate analyses. The first set of analyses adjusted for potentially confounding variables ascertained at baseline (i.e., age, education, body mass index, alcohol consumption, and physical activity). The second set of analyses was based on a smaller analytic cohort since in addition to the risk factors controlled for in the first set of multivariate analyses, it also controlled for income, age at first birth and family history of breast cancer, the latter two of which were only available for participants of the first follow-up survey.

Lastly, we adjusted the sunlight exposure variables for dietary vitamin D intake. Similarly, the dietary exposure variables were adjusted for sunlight exposure.

2.2. Results

2.2.1. Sunlight exposure and breast cancer risk

Based on histories of occupational and recreational activities, the physicians conducting the baseline dermatologic examination rated each participant's sunlight exposure as considerable (13%), moderate (41%) or unimpressive (46%). When participants in the first follow-up interview were asked to classify their usual occupational and recreational sunlight exposure as frequent, occasional, or rare/none. For occupational sunlight exposure, the corresponding percentages were 26, 25, and 49, respectively, and for recreational sunlight exposure, the percentages were 42, 40, and 19, respectively. Cross-classifying reports on occupational and recreational sunlight exposure, 19% of women had overall high sunlight exposure (frequent - frequent) and 14% of women had overall low exposure (rare/none - rare/none). The remaining women were classified as having had medium sunlight exposure.

Age-adjusted relative risks associated with physician-determined and self-reported usual sunlight exposure are presented in table 3. For all four exposure variables, the risk of breast cancer decreased with increasing sunlight exposure. The magnitude of risk reduction associated with high sunlight exposure was similar for the physician-determined measure (RR = 0.60, 95% CI = 0.33-1.09) and the overall exposure index derived from self-report (RR = 0.54, 95% CI = 0.28-1.02).

Although not considered a direct measure of sunlight exposure, hair color was associated with breast cancer risk (table 4). Compared to women with blonde or red hair, reduced risks, although not statistically significant, were observed for women with brown or black hair. Compared to women with blue eyes, reduced risks for also observed for women with gray, green, or hazel eyes or dark brown eyes, but not for women with light brown eyes.

Thirteen percent of the analytic cohort had moderate or severe actinic skin damage as assessed during the baseline dermatologic examination. Moderate or severe elastosis, telangiectasia, or keratosis were found in 10%, 9%, and 3%, respectively. Associations with actinic skin damage are presented in table 5. Overall skin damage was not associated with breast cancer risk. A relative risk of 0.65 (95% CI = 0.36-1.19) was found for women with moderate or severe elastosis. The relative risk for moderate or severe keratosis was also below 1.0, but based on only three breast cancer cases with that condition. Moderate or severe telangiectasia, on the other hand, was associated with an increased risk of breast cancer (RR = 1.41, 95% CI = 0.86-2.33).

Women who participated in the baseline interview were evenly spread across the US, with about 25% living in each of the four regions. The distribution by level of solar radiation (high, medium, low) in the state of longest residence was 28%, 30%, and 42%, respectively. Similar to the direct measures of sunlight exposure, high residential solar radiation was also associated with significantly reduced breast cancer risk. Residence in the South at baseline (RR = 0.59, 95% CI = 0.35-0.98), longest residence in a state of high solar radiation (RR = 0.59, 95% CI = 0.36-0.94), and being

born in a state of high solar radiation (RR=0.53, 95% CI=0.32-0.87) were associated with similar reductions in risk, ranging from 41-47%. Restricting the analysis to women who lived 20 or more years or more than half their life-time in the state of longest residence produced very similar relative risks.

2.2.2. Dietary vitamin D and breast cancer risk

The average vitamin D intake, as assessed by the 24-hour dietary recall, was slightly lower among the 127 breast cancer cases (137 IU) compared to the 4,553 women without breast cancer (148 IU). The difference, however, was not statistically significant. Compared to the recommended daily allowance (RDA) of 200 IU for women age 23 and older, dietary vitamin D intake was relatively low in this population. Only 20% of breast cancer cases and 27% of women without breast cancer exceeded the RDA. Nearly half of the population had an intake of less than 100 IU.

Classifying women by the quartile distribution of dietary vitamin D intake, the highest intake (207 IU or more) was associated with the lowest relative risk (RR=0.67, 95% CI=0.40-1.11) compared to the lowest intake (less than 44 IU) (table 7). However, there was no consistent trend of decreasing risk with increasing vitamin D intake.

Based on the food frequency questionnaire which assessed the usual consumption during the 3 months preceding the baseline interview, daily consumption of whole milk, skim milk, cheese, and eggs was reported by 39%, 12%, 13%, and 16%, respectively, of the analytic cohort. Sixteen percent consumed fish at least twice a week, although no distinction was made between fatty (rich in vitamin D) and other fish.

The frequency of consumption of whole milk, skim milk, fish, and cheese was not associated with breast cancer risk. A slight risk reduction was observed among women who consumed these foods at least 3 times per week (RR=0.80, 95% C1=0.50-1.28).

2.2.3. Supplement use and breast cancer risk

Seventeen percent of the analytic population reported regular (daily) use of multivitamins, which typically contain 400 IU of vitamin D. An additional 1% reported regular use of single vitamin D. Eight percent of the population used multivitamins on an irregular basis (at least once a week).

Regular supplementation with vitamin D from multivitamins or single vitamins was not associated with reduced breast cancer risk (table 8).

2.2.4. Vitamin D from sunlight exposure and diet and breast cancer risk

Cross-classifying physician-determined sunlight exposure and dietary vitamin D intake derived from the 24-hour dietary recall, 17% of the women had high vitamin D exposure, 50% had medium exposure, and 33% had low exposure. Breast cancer risk decreased with increasing levels of vitamin D exposure. High exposure was associated with a relative risk of 0.68 (95% CI=0.39-1.18).

2.2.5. Adjustment for potential confounding

Associations of breast cancer with other risk factors are shown in table 10. As reported in other populations, breast cancer risk was associated with high education, high income, older age at first birth, family history of breast cancer, and high frequency of alcohol consumption. High level of physical activity was associated with reduced breast cancer risk. Age at menarche, however, was not associated with breast cancer risk in the expected direction. Although an increased risk of breast cancer was observed for women with the highest body mass index, but there was no trend of increasing risk with increasing body mass.

Adjusting each of the relative risks individually for the above risk factors in addition to age, little evidence of confounding was found (data not shown). The relative risks before and after adjustment differed by less than 10%.

Multivariate adjusted relative risks are shown in tables 11-14. For comparison, three sets of relative risks are shown: 1) relative risks adjusted for age only; 2) relative risks adjusted for age, education, body mass index, frequency of alcohol consumption, and physical activity; and 3) relative risks adjusted for age, education, income, age at first birth, body mass index, frequency of alcohol consumption, physical activity, and family history of breast cancer. As noted for univariate adjustment, multivariate adjustment only minimally changed the age-adjusted relative risk estimates.

Tables 15 and 16 present relative risks associated with sunlight exposure variables, adjusted for age and dietary vitamin D intake. Table 17 shows relative risks associated with dietary vitamin D intake, adjusted for sunlight exposure. In both sets of analyses there was little evidence of confounding.

3. DISCUSSION AND CONCLUSIONS

Our findings of reduced breast cancer risk among white women with high sunlight exposure, high residential solar radiation, and high dietary vitamin D intake, support the hypothesis that vitamin D may protect against the development of breast cancer. Women with high vitamin D exposure had a 30-50% reduction in breast cancer risk. The results were not explained by differential distributions of other risk factors. Statistical control for confounding by several other risk factors produced only small changes in relative risk estimates.

Most previous studies that addressed the vitamin D hypothesis presented ecologic correlations or risk estimates for a single component of vitamin D exposure (e.g., milk, fish). To our knowledge, this is the first study to examine the relationship between breast cancer risk and sunlight exposure. Furthermore, this is the first study to consider vitamin D derived from multiple sources (i.e., sunlight, diet, and supplements). Reduced breast cancer risks were associated both with high sunlight exposure and high dietary vitamin D intake, but not with vitamin D from supplement use.

Dietary vitamin D intake in the United States is relatively low, particularly among the elderly [53-55]. In this national cohort of women aged 25-74 years, only about 25% of women had an intake exceeding the Recommended Daily Allowance of 200 IU for women age 23 and older.

The NHANES surveys offered a cost-effective approach to explore a new hypothesis using already collected data. While information on several vitamin D related variables was collected, our analyses were limited by the type of data collected at baseline. For example, the available data did not allow us to assess the association with lifetime patterns of sunlight exposure or sunlight exposure during specific periods of life that may be critical in the development of breast cancer. Similarly, a single 24-hour dietary recall may not be a reflection of lifetime dietary patterns. Future studies addressing the vitamin D hypothesis need to apply improved methods to assess vitamin D exposure from multiple sources. Although this analysis was based on data collected for a large national cohort of women, the analytic population included only 133 breast cancer cases, thus limiting subgroup analyses. Confirmation of our results in larger studies using improved exposure assessment methodologies is warranted.

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Esther M. John, Ph.D.

Table 1:   Analytic cohort

Total number of women in NHEFS follow-up study	**8,596**
No follow-up interview	814
Prior history of malignancy	235
Ambiguous breast cancer cases *	35
Prevalent breast cancer cases (diagnosed prior to baseline interview)	15
Eligibles	**7,497**
Women without breast cancer	7,307
Women with breast cancer	190
Self-report confirmed by hospital records	148
Proxy report confirmed by death certificate	5
Death certificate only	4
Self-report only	33
Eligibles with dermatology and dietary assessment	**5,944**
Women without breast cancer	5,787
Women with breast cancer	157

Table 2: Demographic characteristics of analytic cohort (N = 5,944):
age at baseline and racial background

	Women with breast cancer	Women without breast cancer
Whites	133	4,748
25-49 years	63	2,719
50-74 years	70	2,029
Blacks	24	989
25-49 years	16	583
50-74 years	8	406
Other	0	50
25-49 years	0	43
50-74 years	0	7
Total	157	5,787

Table 3: Sunlight exposure and breast cancer
White women

	Breast cancer cases	Person-years	RR and 95% CI adjusted for age (years)
MD determined sunlight exposure	N = 133		
unimpressive	71	30,557	1.0
moderate	49	26,929	0.77 (0.54-1.11)
considerable	13	8,712	0.60 (0.33-1.09)
Usual recreational sunlight exposure *	N = 109		
rare/never	29	11,065	1.0
occasional	38	23,708	0.72 (0.44-1.17)
frequent	42	25,201	0.73 (0.45-1.18)
Usual occupational sunlight exposure *	N = 108		
rare/never	61	29,339	1.0
occasional	25	14,907	0.78 (0.49-1.23)
frequent	22	15,714	0.58 (0.36-0.95)
Overall sunlight exposure (recreational and occupational)	N = 108		
low	22	8,189	1.0
medium	70	40,277	0.74 (0.46-1.20)
high	16	11,453	0.54 (0.28-1.02)

*   Based on self-reports from 1982-84 interview

Table 4: Personal characteristics and breast cancer risk
White women

	Breast cancer cases	Person-years	RR and 95% CI adjusted for age (years)
Natural hair color at age 20	N = 132		
red or blonde	23	9,725	1.0
medium or light brown	52	24,862	0.86 (0.53-1.41)
dark brown	43	24,509	0.75 (0.45-1.25)
black	14	6,524	0.85 (0.44-1.64)
Eye color	N = 132		
blue	53	20,315	1.0
gray, green or hazel	34	22,343	0.63 (0.41-0.97)
light brown	19	7,643	1.00 (0.59-1.69)
dark brown	26	15,664	0.72 (0.45-1.16)

Table 5: Actinic skin damage and breast cancer
White women

	Beast cancer cases	Person-years	RR and 95% CI adjusted for age (years)
Overall actinic skin damage at baseline	N = 133		
normal	76	42,840	1.0
minimal	36	15,759	0.97 (0.64-1.47)
moderate or severe	21	7,866	1.01 (0.60-1.68)
Elastosis	N = 133		
normal	101	51,648	1.0
minimal	19	8,640	0.80 (0.48-1.32)
moderate or severe	13	6,177	0.65 (0.36-1.19)
Keratosis	N = 133		
normal	124	60,542	1.0
minimal	6	4,381	0.45 (0.19-1.04)
moderate or severe	3	1,542	0.60 (0.19-1.92)
Telangiectasia	N = 133		
normal	90	49,382	1.0
minimal	23	11,307	0.85 (0.53-1.36)
moderate or severe	20	5,776	1.41 (0.86-2.33)

Table 6: Residential sunlight exposure and breast cancer risk
White women

	Breast cancer cases	Person-years	RR and 95% CI adjusted for age (years)
Region of residence at baseline	N = 133		
Northeast	35	14,705	1.0
Mid-west	36	17,056	0.89 (0.56-1.42)
West	37	17,994	0.85 (0.53-1.35)
South	25	16,710	0.59 (0.35-0.98)
Solar radiation*: state of longest residence	N = 131		
low	60	27,470	1.0
medium	48	19,658	1.11 (0.76-1.62)
high	23	18,175	0.59 (0.36-0.94)
Solar radiation: state of longest residence for 20+ years	N = 115		
low	55	25,051	1.0
medium	40	17,573	1.02 (0.68-1.53)
high	20	16,172	0.56 (0.34-0.94)
Solar radiation: state of longest residence for 50+ % of lifetime	N = 112		
low	55	25,641	1.0
medium	37	18,117	0.95 (0.63-1.44)
high	20	16,490	0.57 (0.34-0.95)
Solar radiation: state of birth	N = 125		
low	59	25,425	1.0
medium	46	21,129	0.92 (0.63-1.34)
high	20	16,597	0.53 (0.32-0.87)

*   Average daily total global radiation (in Langleys) per day.

low: < 304 Langleys

medium: 305-365 Langleys

high: > = 366 Langleys

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Table 7: Dietary vitamin D and breast cancer risk
White women only

	Breast cancer cases	Person-years	RR and 95% CI adjusted for age (years)
Vitamin D intake from food *	N = 127		
very low (< 44 IU)	37	15,847	1.0
low (44-110 IU)	30	16,135	0.76 (0.47-1.23)
medium (111-206 IU)	35	15,763	0.92 (0.58-1.46)
high (207+ IU)	25	16,173	0.67 (0.40-1.11)
Whole milk **	N = 126		
never or <1 /wk	38	20,743	1.0
1-6 /wk	40	18,187	1.22 (0.78-1.90)
7+ /wk	48	24,919	1.06 (0.70-1.63)
Skim milk **	N = 126		
never or <1 /wk	97	49,965	1.0
1-6 /wk	13	6,515	0.93 (0.52-1.66)
7+ /wk	16	7,334	1.03 (0.60-1.74)
Fish **	N = 126		
never or <1 /wk	50	28,959	1.0
1 /wk	57	24,775	1.44 (0.98-2.11)
2+ /wk	19	10,136	1.17 (0.69-1.99)
Eggs **	N = 126		
never or <1 /wk	26	11,458	1.0
1-2 /wk	50	23,822	0.97 (0.60-1.56)
3+ /wk	50	28,576	0.81 (0.50-1.30)
Cheese **	N = 126		
never or <1 /wk	19	10,456	1.0
1-2 /wk	53	25,312	1.28 (0.75-2.16)
3+ /wk	54	28,068	1.17 (0.69-1.97)

*   dietary intake during 24 hours preceeding baseline interview

**   frequency of consumption during 3 months preceding baseline interview

Table 8: Vitamin D from supplements and breast cancer risk
White women only

	Breast cancer cases	Person-years	RR and 95% CI adjusted for age (years)
Multivitamins	N = 127		
never	98	47,949	1.0
irregular	9	5,021	0.87 (0.54-1.41)
regular	20	11,070	0.93 (0.47-1.84)
Multivitamins or single vitamin D	N = 127		
never	96	47,471	1.0
irregular	9	5,123	0.93 (0.58-1.47)
regular	22	11,446	0.91 (0.46-1.81)

Table 9: Vitamin D from sunlight exposure and diet and breast cancer risk
White women only

	Breast cancer cases	Person-years	RR and 95% CI adjusted for age (years)
Vitamin D (from diet and sun exposure) *	N = 127		
low	49	21,348	1.0
medium	61	31,882	0.80 (0.55-1.17)
high	17	10,810	0.68 (0.39-1.18)

* high: > = 207 IU from diet and moderate sunlight exposure (MD determined) or
> = 111 IU from diet and considerable sunlight exposure.

  low: < = 110 IU from diet and unimpressive sunlight exposure or
< = 43 IU from diet and moderate sunlight exposure

Table 10. Breast cancer risk and other risk factors
White women

	Breast cancer cases	RR (95% CI) adjusted for age (years)
Education		
< 12 years	53	1.0
12 years (HS grad)	45	1.07 (0.70-1.62)
> 12 years	36	1.54 (1.00-2.39)
Marital status		
not married	43	1.0
married	91	0.95 (0.64-1.39)
Income		
1 (low)	22	1.0
2	25	0.92 (0.52-1.64)
3	33	1.21 (0.70-2.09)
4 (high)	50	1.74 (1.05-2.90)
Age at menarche		
14+ years	52	1.0
12-13 years	69	0.67 (0.35-1.27)
<12 years	12	0.94 (0.97-1.40)
Age at first live birth		
<20	33	1.0
20-24	48	1.23 (0.79-1.92)
25-29	24	1.47 (0.87-2.49)
30+	11	1.46 (0.74-2.89)
nulliparous		
Family history of BC		
no	112	1.0
yes	14	2.03 (1.16-3.54)
Body mass index		
1 (low)	26	1.0
2	41	1.36 (0.83-2.22)
3	32	1.07 (0.63-1.81)
4 (high)	35	1.36 (0.81-2.28)

Table 10. Continued

	Breast cancer cases	RR (95% CI) adjusted for age (years)	
Frequency of alcohol consumption in past year			
less than monthly/never	73	1.0	
weekly/monthly	48	1.51	(1.04-2.20)
daily/almost daily	13	1.65	(0.91-2.97)
Recreational physical activity			
little or none	73	1.0	
moderate	45	0.83	(0.58-1.21)
much	16	0.74	(0.43-1.27)
Occupational physical activity			
inactive	14	1.0	
moderate	65	0.83	(0.46-1.47)
very active	55	0.81	(0.45-1.46)
Overall physical activity (recreational and occupational)			
low	52	1.0	
medium	47	0.81	(0.54-1.20)
high	35	0.78	(0.51-1.21)

Table 11: Sunlight exposure and breast cancer risk: multivariate analyses
White women

	#BC*	RR and 95% CI adjusted for age (years)	#BC*	RR and 95% CI adjusted for **	#BC*	RR and 95% CI adjusted for ***
MD determined sun exposure	133		133		120	
unimpressive		1.0		1.0		1.0
moderate		0.77 (0.54-1.11)		0.75 (0.52-1.09)		0.85 (0.58-1.25)
considerable		0.60 (0.33-1.09)		0.61 (0.34-1.11)		0.66 (0.35-1.23)
Recreational sunlight exposure	109		109		104	
rare or never		1.0		1.0		1.0
occasional		0.72 (0.44-1.17)		0.70 (0.43-1.14)		0.74 (0.44-1.22)
frequent		0.73 (0.45-1.18)		0.73 (0.45-1.19)		0.79 (0.48-1.31)
Occupational sunlight exposure	108		108		103	
rare or never		1.0		1.0		1.0
occasional		0.78 (0.49-1.23)		0.79 (0.50-1.26)		0.80 (0.49-1.31)
frequent		0.58 (0.36-0.95)		0.63 (0.38-1.04)		0.65 (0.39-1.09)
Overall sunlight exposure (recreational and occupational)	108		108		103	
rare or never		1.0		1.0		1.0
occasional		0.74 (0.46-1.20)		0.73 (0.45-1.18)		0.72 (0.44-1.18)
frequent		0.54 (0.28-1.02)		0.56 (0.29-1.08)		0.56 (0.29-1.10)
Overall skin damage	133		133		120	
normal		1.0		1.0		1.0
minimal		0.97 (0.64-1.47)		0.96 (0.63-1.46)		0.88 (0.56-1.37)
moderate/ severe		1.01 (0.60-1.68)		1.02 (0.61-1.71)		0.99 (0.58-1.71)
Elastosis	133		133		120	
normal		1.0		1.0		1.0
minimal		0.80 (0.48-1.32)		0.82 (0.49-1.36)		0.74 (0.42-1.28)
moderate/ severe		0.65 (0.36-1.19)		0.69 (0.38-1.27)		0.70 (0.37-1.32)

*   Number of breast cancer cases included in the analysis.

**   Adjusted for age, education, body mass index, frequency of alcohol consumption, and physical activity.

***   Adjusted for age, education, income, age at first birth, body mass index, frequency of alcohol consumption, physical activity, and family history of breast cancer.

Table 12: Residential sunlight exposure and breast cancer risk: multivariate analyses
White women

	#BC *	RR and 95% CI adjusted for age (years)	#BC *	RR and 95% CI adjusted for **	#BC *	RR and 95% CI adjusted for ***
Region of residence	133		133		120	
Northeast		1.0		1.0		1.0
Midwest		0.89 (0.56-1.42)		0.91 (0.57-1.46)		0.92 (0.56-1.50)
West		0.85 (0.53-1.35)		0.83 (0.52-1.32)		0.82 (0.50-1.36)
South		0.59 (0.35-0.98)		0.64 (0.38-1.08)		0.64 (0.37-1.13)
Solar radiation at longest residence	131		131		120	
low		1.0		1.0		1.0
medium		1.11 (0.76-1.62)		1.16 (0.79-1.69)		1.10 (0.74-1.65)
high		0.59 (0.36-0.94)		0.60 (0.37-0.97)		0.65 (0.39-1.08)
Solar radiation at place of birth	125		125		120	
low		1.0		1.0		1.0
medium		0.92 (0.63-1.34)		0.95 (0.65-1.39)		0.94 (0.63-1.40)
high		0.53 (0.32-0.87)		0.55 (0.33-0.91)		0.60 (0.35-1.02)

* Number of breast cancer cases included in the analysis.

** Adjusted for age, education, body mass index, frequency of alcohol consumption, and physical activity.

*** Adjusted for age, education, income, age at first birth, body mass index, frequency of alcohol consumption, physical activity, and family history of breast cancer.

Table 13: Dietary vitamin D and breast cancer risk: multivariate analyses
White women

	#BC*	RR and 95% CI adjusted for age (years)	#BC*	RR and 95% CI adjusted for **	#BC*	RR and 95% CI adjusted for ***
Dietary vitamin D intake	127		127		114	
very low		1.0		1.0		1.0
low		0.76 (0.47-1.23)		0.78 (0.48-1.26)		0.89 (0.53-1.47)
medium		0.92 (0.58-1.46)		0.93 (0.59-1.48)		0.97 (0.59-1.59)
high		0.67 (0.40-1.11)		0.70 (0.42-1.16)		0.73 (0.42-1.26)

*   Number of breast cancer cases included in the analysis.

**   Adjusted for age, education, body mass index, frequency of alcohol consumption, and physical activity.

***   Adjusted for age, education, income, age at first birth, body mass index, frequency of alcohol consumption, physical activity, and family history of breast cancer.

Table 14: Vitamin D from sunlight exposure and diet
and breast cancer risk: multivariate analyses
White women

	#BC *	RR and 95% CI adjusted for age (years)	#BC *	RR and 95% CI adjusted for **	#BC *	RR and 95% CI adjusted for ***
Vitamin D (from diet and sun exposure)	127		126		113	
low		1.0		1.0		1.0
medium		0.80 (0.55-1.17)		0.81 (0.55-1.19)		0.86 (0.57-1.28)
high		0.68 (0.39-1.18)		0.70 (0.40-1.22)		0.74 (0.41-1.31)

*   Number of breast cancer cases included in the analysis.

**   Adjusted for age, education, body mass index, frequency of alcohol consumption, and physical activity.

***   Adjusted for age, education, income, age at first birth, body mass index, frequency of alcohol consumption, physical activity, and family history of breast cancer.

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Table 15: Sunlight exposure and breast cancer risk: adjusted for dietary vitamin D
White women

	#BC *	RR and 95% CI adjusted for age (years)	#BC *	RR and 95% CI adjusted for age and dietary vitamin D intake (quartiles)
MD determined sun exposure	133		126	
unimpressive		1.0		1.0
moderate		0.77 (0.54-1.11)		0.77 (0.53-1.11)
considerable		0.60 (0.33-1.09)		0.59 (0.32-1.09)
Recreational sunlight exposure **	109		103	
rare or never		1.0		1.0
occasional		0.72 (0.44-1.17)		0.82 (0.49-1.37)
frequent		0.73 (0.45-1.18)		0.86 (0.52-1.42)
Occupational sunlight exposure **	108		102	
rare or never		1.0		1.0
occasional		0.78 (0.49-1.23)		0.76 (0.47-1.23)
frequent		0.58 (0.36-0.95)		0.62 (0.38-1.02)
Overall sunlight exposure (recreational and occupational) **	108		102	
rare or never		1.0		1.0
occasional		0.74 (0.46-1.20)		0.84 (0.50-1.41)
frequent		0.54 (0.28-1.02)		0.63 (0.32-1.24)

*   Number of breast cancer cases included in the analysis.

**   Based on self-reports from 1982-84 interview.

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Table 16: Residential sunlight exposure and
breast cancer risk: adjusted for dietary vitamin D
White women

	#BC *	RR and 95% CI adjusted for age (years)		#BC *	RR and 95% CI adjusted for age and dietary vitamin D intake (quartiles)	
Region of residence	133			126		
Northeast		1.0			1.0	
Midwest		0.89	(0.56-1.42)		0.98	(0.60-1.60)
West		0.85	(0.53-1.35)		1.01	(0.62-1.63)
South		0.59	(0.35-0.98)		0.65	(0.38-1.11)
Solar radiation at longest residence	131			126		
low		1.0			1.0	
medium		1.11	(0.76-1.62)		1.17	(0.80-1.73)
high		0.59	(0.36-0.94)		0.66	(0.40-1.07)
Solar radiation at place of birth	125			126		
low		1.0			1.0	
medium		0.92	(0.63-1.34)		0.94	(0.64-1.39)
high		0.53	(0.32-0.87)		0.55	(0.33-0.92)

*   Number of breast cancer cases included in the analysis.

Table 17. Dietary vitamin D and breast cancer risk: adjusted for sunlight exposure
White women

	#BC*	RR and 95% CI adjusted for age (years)	#BC*	RR and 95% CI adjusted for age and MD-determined sunlight exposure	#BC*	RR and 95% CI adjusted for age and solar radiation at longest residence
Dietary vitamin D intake	127		126		126	
very low		1.0		1.0		1.0
low		0.76 (0.47-1.23)		0.76 (0.47-1.24)		0.76 (0.47-1.23)
medium		0.92 (0.58-1.46)		0.90 (0.56-1.43)		0.89 (0.56-1.42)
high		0.67 (0.40-1.11)		0.68 (0.41-1.13)		0.68 (0.41-1.12)

*   Number of breast cancer cases included in the analysis.

LIST OF PERSONNEL

Esther M. John, Ph.D., Principal Investigator
Jocelyn Koo, Statistical analyst
Darlene Dreon, Ph.D., Consultant
Gary Schwartz, Ph.D., Consultant